PHARMACEUTICAL COMPOSITION AND METHOD FOR TREATING HYPOGONADISM

FIELD OF THE INVENTION

The present invention is directed to a pharmaceutical composition comprising testosterone in a gel formulation, and to methods of using the same.

BACKGROUND OF THE INVENTION

A. Testosterone Metabolism in Men

Testosterone is the major circulating androgen in men. More than 95% of the 6–7 mg of testosterone produced per day is secreted by the approximately 500 million Leydig cells in the testes. Two hormones produced by the pituitary gland, luteinizing hormone ("LH") and follicle stimulating hormone ("FSH"), are required for the development and maintenance of testicular function.

The most important hormone for the regulation of Leydig cell number and function is LH. In eugonadal men, LH secretion from the pituitary is inhibited through a negative-feedback pathway by increased concentrations of testosterone through the inhibition of the release of gonadotropin-releasing hormone ("GRH") by the hypothalamus. FSH promotes spermatogenesis and is essential for the normal maturation of sperm. FSH secretion from the pituitary normally is inhibited through a negative-feedback pathway by increased testosterone concentrations.

Testosterone is responsible primarily for the development and maintenance of secondary sex characteristics in men. In the body, circulating testosterone is metabolized to various 17-keto steroids through two different pathways. Testosterone can be metabolized to dihydrotestosterone ("DHT") by the enzyme 5α-reductase. There are two forms of 5α-reductase in the body: one form is found predominately in the liver and non-genital skin while another form is found in the urogenital tract of the male and the genital skin of both sexes. Testosterone can also be metabolized to estradiol ("E_2") by an aromatase enzyme complex found in the liver, fat, and the testes.

Testosterone circulates in the blood 98% bound to protein. In men, approximately 40% of the binding is to the high-affinity sex hormone binding globulin ("SHBG"). The remaining 60% is bound weakly to albumin. Thus, a number of measurements for testosterone are available from clinical laboratories. The term "free" testosterone as used herein refers to the fraction of testosterone in the blood that is not bound to protein. The term "total testosterone" or "testosterone" as used herein means the free testosterone plus protein-bound testosterone. The term "bioavailable testosterone" as used herein refers to the non-SHBG bound testosterone and includes testosterone weakly bound to albumin.

The conversion of testosterone to DHT is important in many respects. For example, DHT binds with greater affinity to SHBG than does testosterone. In addition, in many tissues, the activity of testosterone depends on the reduction to DHT, which binds to cytosol receptor proteins. The steroid-receptor complex is then transported to the nucleus where it initiates transcription and cellular changes related to androgen action. DHT is also thought to lower prostate volume and inhibit tumor development in the prostate. Thus, given the importance of DHT and testosterone in normal body functioning, researchers frequently assess and report androgen concentrations in patients as total androgen ("DHT+T") or as a ratio of DHT to testosterone ("DHT/T ratio").

The following table from the UCLA-Harbor Medical Center summarizes the hormone concentrations in normal adult men range:

TABLE 1

Hormone Levels in Normal Men

Hormone	Normal Range
Testosterone	298 to 1043 ng/dL
Free testosterone	3.5 to 17.9 ng/dL
DHT	31 to 193 ng/dL
DHT/T Ratio	0.052 to 0.33
DHT + T	372 to 1349 ng/dL
SHBG	10.8 to 46.6 nmol/L
FSH	1.0 to 6.9 mlU/mL
LH	1.0 to 8.1 mlU/mL
E_2	17.1 to 46.1 pg/mL

There is considerable variation in the half-life of testosterone reported in the literature, ranging from 10 to 100 minutes. Researchers do agree, however, that circulating testosterone has a diurnal variation in normal young men. Maximum levels occur at approximately 6:00 to 8:00 a.m. with levels declining throughout the day. Characteristic profiles have a maximum testosterone level of 720 ng/dL and a minimum level of 430 ng/dL. The physiological significance of this diurnal cycle, if any, however, is not clear.

B. Hypogonadal Men and Current Treatments for Hypogonadism

Male hypogonadism results from a variety of pathophysiological conditions in which testosterone concentration is diminished below the normal range. The hypogonadic condition is sometimes linked with a number of physiological changes, such as diminished interest in sex, impotence, reduced lean body mass, decreased bone density, lowered mood, and energy levels.

Researchers generally classify hypogonadism into one of three types. Primary hypogonadism includes the testicular failure due to congenital or acquired anorchia, XYY Syndrome, XX males, Noonan's Syndrome, gonadal dysgenesis, Leydig cell tumors, maldescended testes, varicocele, Sertoli-Cell-Only Syndrome, cryptorchidism, bilateral torsion, vanishing testis syndrome, orchiectomy, Klinefelter's Syndrome, chemotherapy, toxic damage from alcohol or heavy metals, and general disease (renal failure, liver cirrhosis, diabetes, myotonia dystrophica). Patients with primary hypogonadism show an intact feedback mechanism in that the low serum testosterone concentrations are associated with high FSH and LH concentrations. However, because of testicular or other failures, the high LH concentrations are not effective at stimulating testosterone production.

Secondary hypogonadism involves an idiopathic gonadotropin or LH-releasing hormone deficiency. This type of hypogonadism includes Kallman's Syndrome, Prader-Labhart-Willi's Syndrome, Laurence-Moon-Biedl's Syndrome, pituitary insufficiency/adenomas, Pasqualini's Syndrome, hemochromatosis, hyperprolactinemia, or pituitary-hypothalamic injury from tumors, trauma, radiation, or obesity. Because patients with secondary hypogonadism do not demonstrate an intact feedback pathway, the lower testosterone concentrations are not associated with increased LH or FSH levels. Thus, these men have low testosterone serum levels but have gonadotropins in the normal to low range.

Third, hypogonadism may be age-related. Men experience a slow but continuous decline in average serum test-